REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks:

STATUS OF CLAIMS

Claims 22, 25, 30-33, 35 and 55-58 are now in this application. Claims 1-18 were previously cancelled. Claims 19-21, 23, 24, 26-29, 34 and 36-54 have been cancelled by the foregoing amendment. Claims 22, 25, 30-33 and 35 are amended hereinabove and claims 55-58 are newly added.

SUPPORT FOR NEW CLAIMS

Claim 55 is the new independent claim, replacing claim 19. Claim 55 is drawn to a method for replicating native or recombinant vaccinia virus, a feature found in previous claim 20 and in original PCT claim 1 and the as-filed specification (as well as in priority application EP 03291813.8, filed July 22, 2003). In addition, the features of former claim 24 (original PCT claim 1) have been introduced to better define and clarify what was meant by the expression "avian embryonic derived stem cells" in former claim 19. Claims 19 and 24 have accordingly been cancelled.

Further with respect to claim 55, in part a) of the method for producing said "avian embryonic derived stem cells" introduced into new claim 55, the previous wording "in a medium containing all the factors allowing their growth and an inactivated feeder layer" in claim 24 has been clarified. The support for this

modification can be found in the as-filed specification, page 4, lines 13-17 and page 5, lines 11-16.

The wording "inoculating avian embryonic derived stem cells with viral particles" in claim 24 have been replaced in claim 55 by "inoculating the resultant avian embryonic derived stem cells with viral particles of said vaccinia virus" to better clarify what is intended by "viral particles". It is obvious from the description and from the examples of the as-filed specification that the viral particles used for the inoculation are viral particles from the virus which it is desired to replicate by the method of the invention; see Example 12, page 27, line 23 of the as-filed specification ("... infected with the virus of interest ...").

New claim 56 has support on page 5, lines 3-5 of the as-filed specification, where it is indicated that chicken and duck are included in the term "avian".

Sufficiency of disclosure and support for guidance to replicate vaccinia virus in avian embryonic derived stem cells obtained from chicken can be found in the as-filed specification as well as in the priority document EP 03291813.8 filed on July 22, 2003; see Examples 1 to 14, particularly in Example 14 where replication of MVA vaccinia virus is carried out on EB14 cell lines (derived from chicken embryonic stem cells).

Applicants are providing herewith further support for demonstrating that the method for replicating vaccinia virus according to the present invention as described herein also provides adequate guidance to replicate vaccinia virus in other avian embryonic stem cell species than chicken; see the appended "Annex 1", Figure 3 and "Annex 2". These additional results show that the guidance to replicate vaccinia virus in chicken embryonic derived stem cells provided by the present patent

application can be used for obtaining vaccinia virus replication in other avian embryonic derived stem cell species such as in duck avian species. If the Examiner wants these additional results to be presented in the form of a 37 C.F.R. § 1.132 declaration, he is requested to so advise the undersigned by telephone so that an appropriate declaration can be promptly prepared and filed.

New claim 57 corresponds to the preferred "feeder layer" indicated in a) of new claim 55 and is supported at least by page 4, lines 15-17, of the as-filed specification.

New claim 58 finds support in the former claim 29 and in the Examples.

In view of the foregoing, applicants submit that the claims as set forth hereinabove do not introduce new matter and are moreover fully enabled by the as-filed specification.

THE DRAWINGS

The acceptance of the drawings by the Examiner is noted, with appreciation.

PRIORITY UNDER 35 U.S.C. § 119

Applicants appreciate the Examiner's acknowledgment of the claim for foreign priority and receipt of copies of the certified copies of the priority documents in this national phase application.

INFORMATION DISCLOSURE STATEMENTS

Applicants acknowledge and thank the Examiner for considering their First and Second Information Disclosure Statements. A Third Information Disclosure Statement is filed herein.

CLAIM OBJECTIONS

In view of the cancellation of former claims and the amended language of the claims now in the application, it is believed that all record objections have been overcome or rendered moot.

CLAIM REJECTIONS - 35 U.S.C. § 112, first paragraph

The claimed invention is now directed to a method for replicating vaccinia virus (native or recombinant vaccinia virus) using avian embryonic derived stem cells produced by the method set forth in step 1) of new claim 55.

The first priority document (EP 03291813.8 of July 22, 2003) and the present patent application as originally filed disclose and claim a method for replicating recombinant or native vaccinia virus (which are virus belonging to Poxvirus family, Orthopoxvirus genus; see the enclosed copy of Pastoret et al., 2003, CIMID, 26, pages 343-355, Elsevier Science Ltd, which is listed on the accompanying Form PTO-1449 for the Examiner's convenience.

Modified Vaccinia Ankara virus (MVA) are the vaccinia virus replicated in avian embryonic derived stem cell lines used in the Examples disclosed in the present patent application as filed as well as in its first claimed priority document, EP 03291813.8.

It is well known by the ordinary skilled person that wild type or recombinant MVA can be used as virus vaccine against smallpox; see page 1, line 21 to page 2, line 4 of the as-filed specification.

It is also known to one of ordinary skill in the art to use the disclosed cells, i.e., inoculated with vaccinia virus, to produce vaccine against cancer. See, for example, the enclosed published review Zeh et al., cancer gene therapy, 2002, 9, 1001-1012, which is listed on the accompanying Form PTO-1449 for the Examiner's convenience, disclosing the use of vaccinia virus for the treatment of human cancers.

In view of these facts as well as the data in Annexes 1 and 2 discussed above, and the remarks below relative to the use of vaccinia virus in cancer treatment, Applicants consider that the invention as now claimed has sufficient disclosure and support in the description and satisfies the requirements of 35 U.S.C. § 112, first paragraph.

CLAIM REJECTIONS - 35 U.S.C. § 112, second paragraph

Claims 20 and 23 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite (claim 20) and incomplete (claim 23). These claims have been cancelled. Moreover, the portion of claim 20 incorporated into new independent claim 55 is now correct. Thus, these rejections have been rendered moot.

CLAIM REJECTIONS - 35 U.S.C. § 102

Claims 19, 21, 23, 30-35, 37-40, 43-45 and 50 have been rejected under 35 U.S.C. §102(e) as being anticipated by Barban et al. US2004/017064 A1. While this

document claims a date of priority of December 13, 2002 from a provisional application, it may in fact be entitled only to its December 12, 2003 filing date, which is subsequent to applicants' July 22, 2003 priority date based on EP 03291813.8 and even subsequent to applicants' December 9, 2003 priority date based on FR 0314389. More importantly, this document discloses a method for replicating an Alvac virus, which is a poxvirus which belongs to the avipox genus of Poxvirus, and not to the vaccinia virus as claimed in the present claims.

Moreover, the cited document does not disclose part a) of step 1) of the method of independent claim 55 of the present invention in order to obtain the chicken embryonic derived stem cells EB1 (type of trophics factors and cytokines chosen). Consequently, all of the claims now in this application, which include claim 55 and the claims which depend, directly or indirectly, from claim 55, are free of the record 35 U.S.C. §102 rejection. Withdrawal of the rejection is believed to be in order and is earnestly solicited.

CLAIM REJECTIONS - 35 U.S.C. § 103

All of claims 19-54 have been rejected under 35 U.S.C. §103 as being unpatentable over Lovas and Hollos and Mayr et al in view of Pain et al, Barban et al. and Ferber. Applicants submit that all of the claims now in this application are free of this obviousness rejection. Specifically, none of these documents, alone or in combination, disclose or suggests the application of avian embryonic derived stem cell lines prepared as set forth in part 1) of claim 55 to replicatenative or recombinant vaccinia virus as claimed in the present invention.

Consequently, Applicants consider that the claimed invention as claimed in the claims as set forth hereinabove is novel and inventive over the cited prior art, particularly in view of the Barban et al. cited document.

The main problem that the instant invention intends to solve is to provide avian cell lines defined as « continuous » (that is to say immortal) without transformation or mutation of cell genome by genetic (i.e., insertion of retroviral sequences ...), chemical (treatment with alkylating agents ...) or physical means (i.e., X ray irradiation ...). Indeed, such artificial modifications of cell genome would produce cells inappropriate for industrial use for the production of viral vaccines (e.g., vaccinia-based vaccines ...), because such cells would be tumorigenic and potentially dangerous for the future vaccines.

The difficulty of establishing continuous avian cell lines is illustrated by the fact that pharmaceutical industry has produced for more than 50 years viral vaccines on embryonated chicken eggs or on chicken embryonic fibroblasts (CEFs) derived from embryonated chicken eggs.

The present inventors conceived the idea of deriving new cell lines from avian embryonic stem cells, which are the sole known immortal avian cells that are non-transformed, that is to say non-cancerous. Indeed, as long as such avian stem cells express the telomerase enzyme (also over-expressed in cancerous cells), they keep proliferating, maintain their undifferentiated phenotype and stay genetically stable (that is to say, diploid). Paradoxically, these avian embryonic stem cells remain genetically stable and immortal, unlike cancerous cells which are genetically unstable (i.e polyploidy, chromosomic translocation, etc.) and immortal.

The culture of avian stem cells is not adapted as such to industrial application, specifically for vaccine production, because avian stem cells grow attached to their support on a layer of feeder cells in the presence of animal serum, in expensive cell culture medium containing growth factors (to stimulate the growth of the stem cells and to avoid the differentiation of the stem cells). The inventors developed an original process that allows the progressive withdrawal of these cell culture components (growth factors, feeders cells, animal serum, anchorage dependence ...) and thus adapts the cells to the new cell culture conditions. At the end, the inventors obtained for the very first time avian derived stem cells that kept the remarkable features of stem cells, the main one being the expression of telomerase enzyme, but that gain in addition industrially compliant characteristics such as: ability to grow indefinitely in suspension cell culture, without feeder cells, in animal serum-free and growth factors-free medium.

The process developed by the inventors has these main features/steps:

First there is isolation from avian embryo and culture of avian embryonic stem (ES) cells, in a cell culture medium containing growth factors (cytokines and trophic factors), animal serum, and feeder cells necessary for the growth of avian ES cells. This feature is important because it is necessary to have the exact culture conditions to avoid ES cell differentiation into different cell types and to culture such undifferentiated ES cells for a period of time, long enough to perform the next step of weaning. Then, there are the successive steps of withdrawal of growth factors, feeder cells, animal serum, and optionally adaptation to anchorage-independence cell growth, in order to ultimately obtain avian cell lines derived from embryonic stem cells. These new cell lines named EBx by the Assignee retain stem cell features

(telomerase expression, cell surface markers expression, ...) and in addition display industrially compliant features (suspension cell growth in a medium free of animal serum, growth factors and feeder cells). The inventors have applied such method to derive many chicken EBx cell lines, among them the EB14 or EB45 cell lines cited in the present patent application.

Using the same guidance disclosed in the present application for the chicken embryonic derived stem cells, the inventors have also derived several duck EBx cell lines, such as EB24, by using the method of the invention. This demonstrates that the instant invention is not limited to chicken species, but can be applied to derived EBx cells from avians generally.

In addition to the data in the specification, Annexes 1 and 2 are examples of vaccinia virus replication in chicken and duck EBx cell lines (see appended Annex 1 and Annex 2).

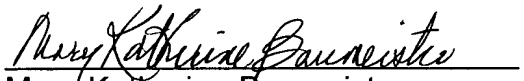
The commercial interest of the instant invention is accredited by the signature of many licences of EBx cell lines to human and animal health pharmaceutical companies such as SANOFI-PASTEUR, GSK, NOVARTIS VACCINES, MERIAL, FORTDODGE, etc. (see www.vivalis.com) for the production of viral vaccines.

In view of the foregoing remarks and the amendments into the claims, Applicants consider that the claims now satisfy all the patentability requirements of the USPTO. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: February 1, 2008

By: 
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

Attachments: Annex 1
Annex 2